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Update on the pharmacological treatment for strabismus

Atualização no tratamento farmacológico do estrabismo

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KEYWORDS:

Botulinum toxin type A; Bupivacaine; Strabismus.

ABSTRACT

Pharmacological treatment is an alternative to surgical treatment for strabismus. Injecting drugs into extraocular muscles is aimed at modifying the balance of forces, providing the correction of strabismus. The main drug used is botulinum toxin whose mechanism of action is blocking the release of acetylcholine during synapses, leading to temporary paralysis of the muscle. Its primary indication is for sixth cranial nerve paralysis/paresis. Moreover, it is used in the treatment of congenital esotropia, particularly for deviations up to 30 prism diopters. Other indications are small deviations, dysthyroid orbitopathy, and patients with cerebral palsy. Recently, the injection of the anesthetic bupivacaine into the muscle has shown satisfactory results in the correction of strabismus. Because its mechanism of action is associated with increased muscle strength and muscle shortening, it is an alternative technique to traditional muscle resection. Treatment with bupivacaine can be performed alone or in combination with the injection of botulinum toxin into the antagonist muscle.

PALAVRAS-CHAVE:

Toxina Botulínica Tipo A; Bupivacaína; Estrabismo.

RESUMO

O tratamento farmacológico é uma alternativa ao tratamento cirúrgico do estrabismo. A injeção de drogas nos músculos oculomotores tem como objetivo modificar o equilíbrio de forças, proporcionando a correção do estrabismo. A principal droga empregada é a toxina botulínica, que apresenta como mecanismo de ação o bloqueio da liberação de acetilcolina na sinapse, levando à paralisia temporária da ação muscular. A principal indicação para seu uso é a paralisia/paresia do sexto nervo craniano. É usada também no tratamento da esotropia congênita, especialmente para desvios até 30 dioptrias prismáticas. Outras indicações são desvios pequenos, orbitopatia distireoidiana e em pacientes com paralisia cerebral. Mais recentemente, a injeção do anestésico bupivacaína dentro do músculo mostrou resultados satisfatórios na correção de estrabismo. Como seu mecanismo de ação é associado a aumento da força e encurtamento do músculo, trata-se de técnica alternativa à tradicional ressecção muscular. O tratamento com bupivacaína pode ser feito isoladamente ou em associação à injeção de toxina botulínica no músculo antagonista.

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INTRODUCTION

Injecting drugs into extraocular muscles has been used for a few years to treat strabismus and is considered by many as the future of strabismus therapy. Behrens was the first to inject a drug (alcohol) into an extraocular muscle with the aim of decreasing its contractile force. Alan Scott, in the early 1970s, began his studies with botulinum toxin type A (BTX-A) to paralyze muscles. Since its approval for clinical use in 1989, the toxin has been used to treat strabismus as an alternative or adjuvant to surgery. More recently, intramuscular bupivacaine injections, alone or in association with BTX-A, have demonstrated satisfactory results in eye alignment because of their strengthening and shortening properties acting on extraocular muscles[1-5].

Botulinum toxin type A

The mechanism of action of BTX-A is blocking the release of acetylcholine during synapses. After metabolizing the toxin, the muscle completely regains its function. The change in eye alignment occurs because, during the paralysis phase, the muscle that received the injection elongates; however, its antagonist shortens, leading to permanent alignment changes[1-2].

When used in paralytic strabismus, BTX-A causes the paralysis of the antagonist to the muscle involved, preventing its contracture. In comitant strabismus, more than one injection may be required, and the effect of BTX-A is shortening the antagonist during the paralysis period. After the effect of the toxin, muscle contraction is recovered under a new balance of forces that allows the alignment of the eyes[3-4].

BTX-A can be injected with the aid of an electromyography needle under topical anesthesia in adults and sedation with ketamine in children. Another method extensively used in Brazil, not requiring an electromyograph, is Mendonça's forceps, which holds the muscle through the intact conjunctiva, facilitating the injection in children and adults[6].

The BTX-A dose and duration of action depends on the manufacturer and preparation. Considering Botox®, the injection takes effect in 2-5 days and lasts from 20 to 90 days. The suggested dose is 2.5U in deviations up to 20PD, 2.5-5.0U in deviations from 20 to 50PD, and 7.5-10.0U for deviations greater than 50PD[6].

After the injection, an overcorrection of the deviation is expected, which improves within a few weeks. Adverse effects of BTX-A include temporary blepharoptosis, which occurs by dispersion of the drug to the levator palpebrae superioris muscle (in up to 50% of cases). Moreover, vertical deviation can temporarily occur (in up to 25% of cases). Severe complications such as ocular perforation, endophthalmitis, and retrobulbar hemorrhage are rare[1,3,6].

The main indications for using BTX-A in treating strabismus are as follows:

Congenital esotropia

The best results described in the literature have been achieved by injection into the two medial rectus muscles, in children aged less than 8 months with moderate angle deviations. Studies demonstrated that, for deviations up to 30PD, the injection has the same success rate as surgery, with a lower rate of long-term overcorrection[7,8]. For ~50% of patients, more than one injection is required to achieve a satisfactory result. The dose-effect relationship seems to change with the age at which the procedure is performed, and the higher the dose used, the greater the chance of failure[7]. For deviations over 30PD, injection presents lower success rates than surgery. In great deviations (≥60PD), BTX-A can be used as an adjuvant to the conventional surgical procedure. In children, BTX-A presents good results, probably attributed to the gain in binocular vision at an early stage of visual development. Another advantage of BTX-A is preserving non-operated muscles for eventual future surgery because it does not alter muscle anatomy[8-10]. However, there is a chance of temporary ptosis occurring in 17%-32% of patients[7].

Paralysis/paresis of the 6th cranial nerve

BTX-A can be used in the acute stage of paralysis, improving the patient's quality of life by allowing binocular vision without diplopia in or near the primary position of gaze. There are controversies about the effect of BTX-A in preventing contracture of the medial rectus muscle, with studies showing the same rate of recovery of lateral rectus muscle strength with or without BTX-A injection into the antagonist muscle. Moreover, BTX-A can be used in the medial rectus muscle prior to horizontal rectus muscle transposition, eliminating the requirement for medial rectus reecession and thus sparing an additional muscle. Thus, ciliary arteries that participate in the irrigation of the anterior segment of the eye are preserved, reducing the risk of postoperative ischemia[1,6].

Other indications

Injection of retrobulbar BTX-A or directly into the four horizontal rectus muscles can be used in treating nystagmus without a head tilt. In acute phases of dysthyroid orbitopathy, BTX-A can be used but at doses higher than usual. In patients with cerebral palsy and esotropia, BTX-A is indicated as an alternative to surgical treatment because of the variability of deviation and the risk of overcorrection as well as possible contraindications to general anesthesia. Other uses are surgical under- or over-corrections and the acute stage of exotropia caused by 3rd nerve paralysis[2,6,11,12].

Alternatives to botulinum toxin

Crotoxin is a neurotoxin from the Crotalus durissus terrificus snake that blocks the release of acetylcholine, causing muscle paralysis. Studies conducted in Brazil with a small number of patients show that crotoxin has effects similar to those of BTX-A in the correction of strabismus; however, additional studies are necessary to confirm its dose-effect relationship and adverse effects[13].

Bupivacaine

Currently, bupivacaine is the only pharmacological treatment available to strengthen and shorten extraocular muscles. Other potential future alternatives are drugs from the group of muscle growth factors, such as insulin-like growth factor, which have been investigated in animals but without clinical application yet[14].

The hypothesis that bupivacaine could contribute to treating strabismus was suggested after cases of strabismus were attributed to its accidental injection into the muscle during retrobulbar block for cataract surgery. The deviation in these patients was initially attributed simply to myotoxicity, but careful observation of clinical evolution suggested that there was a more complex mechanism involving both increased contractility and muscle stiffness[15,16]. When its mechanism of action was better explained, bupivacaine began being used for strabismus treatment as an alternative to surgery. Because its mechanism is associated with increased muscle strength and shortening, it is considered an alternative to muscle resection. While resection sacrifices tissue, treatment with bupivacaine increases contractile and elastic forces, without compromising orbital mechanics nor scarring[5,17].

The mechanism of action of bupivacaine is destroying myofibrils, the specialized structures of muscle cells responsible for contractile and elastic forces, but preserving peripheral nerves, capillaries, basal lamina, and satellite cells. This process induces calcium release by the sarcoplasmic reticulum and inhibits its reception, sensitizing the contractile apparatus to calcium such that, within a few minutes after injection of the drug, there is exaggerated contraction of myofibrils and cell membrane damage. In a few hours, proteases are activated by calcium and cleave sarcomeres, which are digested by macrophages. This damage to muscle tissue releases growth factors of local effects, leading to the activation of satellite cells, which are the local stem cells involved in the process of muscle repair and regeneration. Their proliferation leads to the formation of new muscle fibers, which, in addition to repairing the initial damage, merge into new fibers, causing muscle hypertrophy in a few weeks[18,19].

Soon after the injection, the muscle is anesthetized for up to 24 h. For up to a week, it becomes hypofunctional because of myotoxicity. Then there is progressive improvement for three weeks, with results stabilizing around 30 days after the injection. Studies with magnetic resonance imaging show a transient increase in the cross-sectional diameter of the muscle and thus presumably increased contractile and elastic forces, followed by stable changes in muscle length[17,20].

The muscle into which bupivacaine is applied regenerates to the length in which it is maintained during the regeneration process. A small dose of BTX-A injection into the antagonist muscle, weakening it, prevents the bupivacaine-treated muscle from being stretched during the repair stage. Thus, the rebuilt muscle is shorter, contributing even more to the correction of the deviation. Another possible way to increase the effectiveness of bupivacaine injection is by combining it with vasoconstrictor epinephrine to prolong the time of exposure of the drug to muscle tissue[17,21].

Unlike BTX-A, which can be applied more anteriorly into the muscle and easily diffuses to the region of the myoneural plaque, bupivacaine should be applied throughout the muscle to expose as many fibers as possible to the drug, and primarily to expose its posterior third, which strongly contributes to the power of muscle contraction. The injection is guided by an electromyograph, which records sound signals emitted by the tip of the needle that are activated by

the muscle. For this technique to be successful, the needle is inserted until the ratio between the electromyograph signal and eye movement indicates the proper positioning of the needle for injection. The recommended dose is 20-90mg, obtained from the concentration of 1.50%-3.00% and volume from 1.25 to 3.00ml[17,20].

Bupivacaine has been used for the treatment of strabismus since 2006 in horizontal, comitant deviations of small and moderate magnitude. When associated with BTX-A injection into the antagonist muscle, the correction is approximately twice as greater and can be used in larger deviations[22-24]. The last published case series showed a mean correction of 16PD in 55 patients with esotropia or exotropia who underwent up to three injections. Stable corrections have been described for more than five years. Treatment is not effective in paralyzed, atrophic muscles or when there is a significant restrictive component. Cases with very small deviations and at risk of diplopia if there is inversion after treatment are, for the time being, better corrected surgically[20].

Both botulinum toxin and bupivacaine are drugs with a potential for treating strabismus. The already well-established BTX-A has its indisputable place in treating paralysis/paresis of the sixth cranial nerve and a less consensual place in congenital esotropia and other types of strabismus. However, bupivacaine, which lacks further studies to establish its dose-effect relationship, has a smaller place in the clinical context, but is promising in deviations of small to moderate angles, especially in patients who have undergone multiple previous surgeries and are not willing to undergo a new surgical procedure but wish to correct their deviations.

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